(19) Europäisch s Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 018 136**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **80301053.7**

(22) Date of filing: **02.04.80**

(51) Int. Cl.³: **C 07 D 473/22**, C 07 D 473/20, A 61 K 31/52

(30) Priority: **05.04.79 GB 7912052**
05.06.79 GB 7919505

(43) Date of publication of application: **29.10.80**
Bulletin 80/22

(84) Designated Contracting States: **AT BE CH DE FR GB IT LI NL SE**

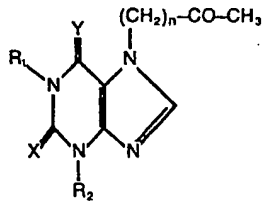
(71) Applicant: **Johann A. Wuelfing, Stresemannallee 6, D-4040 Neuss (DE)**

(72) Inventor: **Goring, Joachim Ewald, Sauerweinstrasse 25, 3212 Gronau (Leine) (DE)**

(74) Representative: **Dawson, Hugh Bainforde, Dr. et al, European Patent Attorney BEECHAM PHARMACEUTICALS Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ. (GB)**

(54) **Xanthine derivatives, a process for their preparation and their use in pharmaceutical compositions.**

(57) Compounds of the formula (II):



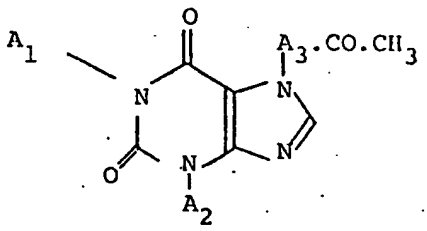
(II)

wherein:
X is sulphur and Y is oxygen or sulphur;
R_1 is an alkyl group of up to 6 carbon atoms;
R_2 is an alkyl group of up to 6 carbon atoms; and
n is 1; or
X is oxygen and Y is sulphur;
one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms; and
n is 1 or 2, having useful pharmacological activity, pro-drugs therefor, a process for their preparation, pharmaceutical compositions containing said compounds or pro-drugs, and intermediate in their preparation of the compounds.

EP 0 018 136 A1

Xanthine Derivatives, a Process for their Preparation and their use in Pharmaceutical Compositions

British Patent Specification No. 1441562 discloses inter alia that compounds such as those of the formula (I):

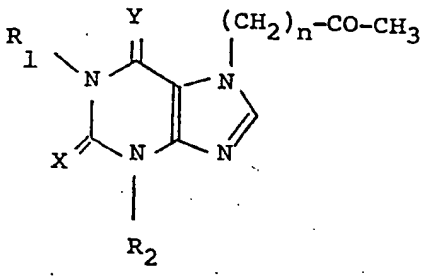


(I)

wherein A_1 and A_2 are alkyl groups and A_3 is an alkylene moiety possess blood flow improving properties. A.K. Armitage et al., British J. Pharmacol., (1961), 17, 202 discloses 7-acetylmethyl-1,3-dimethyl-6-thioxanthine as a bronchodilator and coronary dilator.

It has now been found that a class of compounds yet further removed from naturally occuring xanthines effect an improvement in the metabolic status of ischaemic sketal muscle by increasing oxygen tension and/or contractility in the tissue. The compounds are thus of potential use as agents for the treatment of peripheral vascular diseases such as intermittent claudication.

The present invention provides the structurally distinct compounds of the formula (II):



(II)

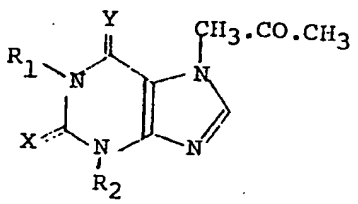
wherein:

X is sulphur and Y is oxygen or sulphur;
R_1 is an alkyl group of up to 6 carbon atoms;
R_2 is an alkyl group of up to 6 carbon atoms; and
n is 1; or

X is oxygen and Y is sulphur;
one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms; and
n is 1 or 2; or a pro-drug therefor.

When used herein the term "pro-drug" means a compound metabolised in vivo to a compound of the formula (I) or its salt. A pro-drug may be identified by administering the pro-drug to a mammal such as a rat, mouse, monkey or man and identifying the compound of the formula (I) or its salt, in for example blood or urine.

When n is 1 or 2, it is preferably 1. Thus, certain particularly suitable compounds of the formula (II) are those of the formula (III):



(III)

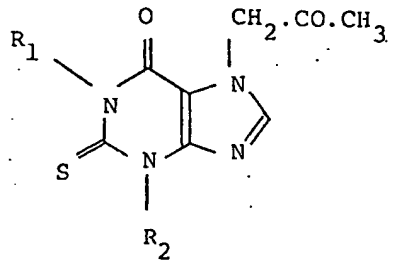
wherein R_1, R_2, X and Y are as defined in relation to formula (II); or a pro-drug therefor.

Alkyl groups R_1 and R_2 worthy of mention for the compounds of the formulae (II) and (III) include the methyl ethyl, iso-propyl, n-butyl, iso-butyl, n-pentyl and n-hexyl groups.

Favourably in formulae (II) and (III) R_1 and R_2 together contain 3 - 10 carbon atoms and more favourably they together contain 4, 5, 6, 7 or 8 carbon atoms.

Aptly Y in the compounds of the formulae (II) and (III) is an oxygen atom and X is a sulphur atom.

Thus certain favoured compounds of this invention include those of the formula (IV), or a pro-drug therefor:



(IV)

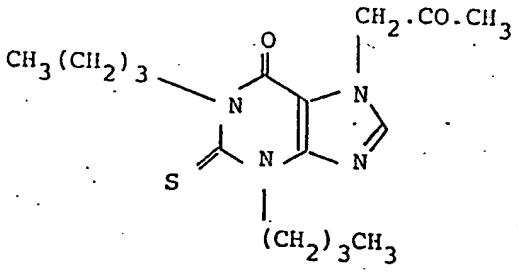
wherein R_1 and R_2 are as defined in formula (II).

Alkyl groups R^1 and R^2 worthy of mention and favourable total carbon atom numbers therefor are as to described under formula (III).

A preferred value for R_1 in formula (IV) is the n-butyl group. Ethyl is also of interest.

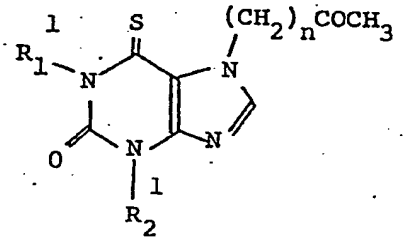
A preferred value for R_2 in formula (IV) is the n-butyl group. Ethyl is also of interest.

From the foregoing it will be appreciated that one compound possessing particularly suitable properties is that of the formula



Also aptly Y in the compounds of the formula (II) is a sulphur atom and X is an oxygen atom.

Thus certain other favoured compounds of this invention include those of the formula (V) or a pro-drug therefor



(V)

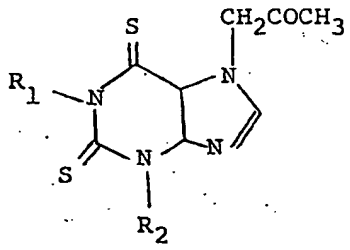
wherein n is as defined in relation to formula (II); and one of R_1^1 and R_2^1 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms.

Suitable groups R_1^1 and R_2^1 include ethyl, iso-propyl, n-butyl, isobutyl, n-pentyl and n-butyl.

Favourably R^1_1 and R^1_2 together contain 4-10 carbon atoms, more favourably 4, 5, 6, 7 or 8 carbon atoms.

Preferably R_1 is butyl and R_2 is ethyl.

Other compounds of this invention are of the formula (VI), or a pro-drug therefor:



(VI)

wherein R_1 and R_2 are as defined in relation to formula (II).

Alkyl groups R_1 and R_2 worthy of mention and favourable total carbon atom numbers therefor are as so described under formula (III).

Preferably R_1 and R_2 are both n-butyl.

Compounds of the formula (II) have useful pharmacological activity, as disclosed hereinbefore, in effecting an improvement in the metabolic status of ischaemic skeletal muscle, by increasing oxygen tension or contractility in the tissue.

Individual compounds of the formula (II) have one or both of these activities. The individual activity profile may be readily ascertained by the two routine pharmacological tests disclosed hereinafter. Nevertheless examples of compounds of interest for each or both activities are given here:

Examples of compounds of the formula (II) which are of particular interest for their activity in increasing ischaemic skeletal muscle contractility are those of the formulae (IV) and (V).

Examples of compounds of the formula (II) which are of particular interest for their activity in increasing oxygen tension in ischaemic skeletal muscle are those of the

formula (VI), in particular 1,3-di-n-butyl-7-(2-oxopropyl)-2,6-thioxanthine.

Examples of compounds of the formula (II) which are of particular interest for both of the foregoing activities are those of the formulae (IV) and (V) having the preferred variable values so described under the relevant formula.

As mentioned hereinbefore the compounds of the formula (II), which have either or both of these activities are of potential use for the treatment of peripheral vascular diseases, such as intermittent claudication.

The present invention therefore also provides a pharmaceutical composition which comprises a compound of the formula (II) or a pro-drug therefor and a pharmaceutically acceptable carrier.

The composition of this invention will normally be provided in the form of a discrete unit dose such as a tablet, capsule or defined quantity of the composition in a form suitable for dissolution to provide an injectable solution. Particularly suitable forms of such compositions are those adapted for oral administration such as tablets or capsules.

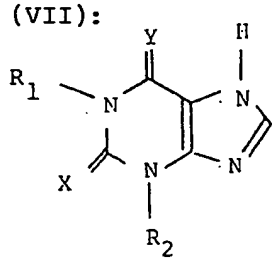
Unit dose compositions of this invention may contain 1 to 500 mgs of active agent. Compounds of this invention wherein the 7-position side chain is other than 2-oxopropyl or a group convertable thereto will normally be present in such compositions in a dose from 100 to 500 mgs, for example 200 to 400 mgs. Compounds of this invention wherein the 7-position side chain is 2-oxopropyl or a group convertable thereto will normally be present in such compositions in a dose of from 1 to 100 mgs, more usually 2.5 to 50 mgs for example 5 to 25 mgs. The unit dose composition will normally be taken from 1 to 4 times daily so that the normal dose for a 70 kg adult human will be

from about 100 to 2000 mgs for a composition containing a compound in which the 7-position substituent is other than 2-oxopropyl or a group convertable thereto and from about 4 to 100 mgs for a composition containing a compound in which the 7-position substituent is a 2-oxopropyl group or a group convertable thereto.

The compositions of this invention may be formulated in conventional manner. Thus oral dosage units may contain such conventional agents as fillers (diluents), lubricants, binders, disintegrants, colourants, flavourings, surface active agents, preservatives, buffering agents, and the like. Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate and the like. Suitable lubricants include stearic acid, magnesium stearate, magnesium lauryl sulphate and the like. Injectable compositions may consist essentially of a sterile, pyrogen free compound of this invention sealed into a vial optionally together with suspending and preserving agents. Such compositions may be made up for administration with sterile water or saline.

The compositions may be prepared by conventional methods of blending, filling, tabletting or the like.

The present invention also provides a process for the preparation of the compounds of this invention which process comprises the reaction of a salt of a compound of the formula (VII):



(VII)

wherein R_1, R_2, X and Y are as defined in relation to

formula (II) with a compound of the formula (VIII):

$$Cl-(CH_2)_n-CO-CH_3 \qquad \text{(VIII)}$$

wherein n and m are as defined in relation to formula (II) or a chemical equivalent thereof.

Suitable chemical equivalents of the chloro-compound of the formula (VIII) include the corresponding bromo- and iodo-compounds and analogous active esters such as mesylates or tosylates.

The salt of the compound of the formula (VII) will normally be an alkali metal salt such as the sodium or potassium salt and may be preformed or generated in situ by the presence of a base such as an hydroxide or ethanolate.

Suitable solvents for use in such processes include lower alkanols such as methanol, ethanol or the like.

The reaction is generally carried out at an ambient or elevated temperature, for example from 20° to 80°C. It is often convenient to carry out the reaction in a solvent under reflux.

When the desired compound has been produced it may be recovered by distilling off the solvent, by precipitation with a miscible non-solvent or the like.

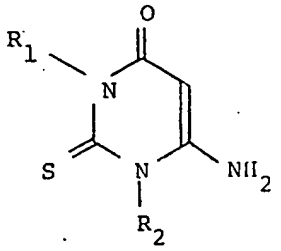
Purification of the compound of this invention may be carried out by conventional methods such as crystallisation, recrystallisation and chromatography.

Compounds of the formula (II) wherein n is 2 may be prepared by the reaction of a compound of the formula (VII) with methyl vinyl ketone or 2-chlorobutan-3-one. This reaction may be carried out under conditions as described herein for reaction with a compound of the formula (VIII).

Certain compounds of the formula (VII) are novel and form part of this invention. Thus the present invention provides the compound of the formula (VII) as hereinbefore described wherein R_1 and R_2 are each n-butyl groups, X is sulphur and O is oxygen or sulphur and salts thereof.

Compounds of the formula (VII) wherein Y is a sulphur atom and X is an oxygen atom may be prepared by the process of K.R.H. Wooldrige and R. Slack, J. Chem. Soc., 1962, 1863-68.

The compounds of the formula (VII) wherein X is a sulphur atom and Y is an oxygen atom may be prepared by the reaction of a compound of the formula (IX):



(IX)

wherein R_1 and R_2 are as defined in relation to formula (II) with sodium carbonate, formamide, formic acid and sodium dithionite. This reaction is generally begun at a depressed temperature such as 3 - 5°C and gradually warmed until completion occurs at an elevated temperature such as 160 - 190°C.

The compounds of formula (IX) may be prepared according to the procedures of Bredeneck et al., Chem. Ber., 88, 1306-1312 (1955). Their conversion into compounds of the formula (VIII) as described above may be viewed in the light of Papesch et al., U.S. Patent No. 2615020.

Compounds of the formula (VII) wherein X and Y are both sulphur atoms may be prepared by the reaction of P_4S_{10} and a compound of the formula (VIII) wherein one of X and Y is a sulphur atom and the other is an oxygen atom

or both of X and Y are oxygen atoms; see for example U.S. patent specification no. 3135753, Chem. Zentralblatt 37-2695 (1966), Chem. Zentralblatt 27-1557 (1966) and Chem. Zentralblatt 40-0983 (1968).

The invention also provides a method for the treatment or prophylaxis of peripheral vascular disease, which method comprises the administration to the sufferer of a therapeutically effective amount of a compound of the formula (II) or a pro-drug therefor.

The following Examples illustrate the invention.

Example 1

1-n-Butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine (1)

1-n-Butyl-3-ethyl-6-thioxanthine (4 g) was dissolved in dimethyl formamide (30 ml) and a small amount of potassium carbonate was added. To this mixture, 1-bromopropan-2-one (2,7 g) was added dropwise at room temperature, with stirring. The reaction was heated at about 50°C for two hours. The reaction mixture was then extracted with chloroform several times, the chloroform phase washed with 1N KOH and water, dried with sodium sulphate, filtered and the chloroform removed in vacuo to yield a red/brown oil which, on crystallisation in a mixture of ethylacetate/petroleum, gave 1-n-butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine as a white powder.

Melting point: 173 - 174°C

Yield: 1 g.

Elemental Analysis

	Calculated	Found
C	54,55	55,14
H	6,49	6,34
N	18,19	17,89
O	10,39	10,60
S	10,39	10,01

Example 2

1,3-Di-n-butyl-7-(3-oxobutyl)-6-thioxanthine (2)

1,3-di-n-butyl-6-thioxanthine (8,3 g), methylvinylketone (2,9 ml) and triethylamine (1 ml) were dissolved in ethanol (10 ml) and the mixture was slowly heated with stirring at 40 - 50°C for one hour. After cooling of the clear solution, the 1,3-di-n-butyl-7-(3-oxobutyl)-6-thioxanthine precipitated in the form of yellow needles.

Melting point: 118 - 119°C

Yield: 8,5 g

Elemental Analysis

	Calculated	Found
C	58,29	58,28
H	7.43	7.40
N	16,00	16,12
O	9,14	9,27
S	9,14	8,90

The structure was confirmed by NMR spectroscopy.

Using an analogous process the following were prepared:

1-n-butyl-3-ethyl-7-(3-oxobutyl)-6-thioxanthine (3), m.pt. 127°C, was prepared in 75% yield. The crystallisation solvent was ethanol.

Elemental Analysis					
	C %	H %	N %	O %	S %
Calculated	55,90	6,83	17,39	9,94	9,94
Found	56,08 55,95	6,91 6,92	16,91 17,03	10,23 10,35	9,87 9,85

1,3-dimethyl-7-(3-oxobutyl)-6-thioxanthine (4), m.pt. 164°C, was prepared in 77% yield. The crystallisation solvent was ethyl acetate/methanol.

Elemental Analysis					
	C %	H %	N %	O %	S %
Calculated	49,62	5,26	21,05	12,03	12,03
Found	49,54 49,46	5,36 5,37	21,29 21,26	11,96 11,96	11,93 11,84

Example 3

1,3-Di-n-butyl-2-thioxanthine (5)

Sodium carbonate (8 g) was dissolved in formamide (200 ml) and 1,3-di-n-butyl-2-thio-4-aminouracil (32 g) was added at a temperature of 3°C with stirring. The mixture was cooled over a period of 1 hour and at a temperature of 3-5°C. Formic acid (16 ml) was added dropwise. The reaction mixture was allowed to stand overnight in a refrigerator. The mixture was then heated to 100°C and then sodium dithionite (5 g) was added at this temperature. To complete the reaction, the mixture was heated to 190°C for 1 hour. After cooling to room temperature with stirring, the oil solidified with crystallisation. The crude product was filtered with suction. To remove coloured by-products, the crude product was dissolved in dilute sodium hydroxide, the solution treated with charcoal and precipitated with acetic acid and the compound was recrystallised from methanol/water to give 1,3-di-n-butyl-2-thioxanthine as white powder.

Melting point: 137°C

Yield: 27,2 g

Elemental Analysis

	Calculated	Found
C	55,69	55,76
H	7,19	7,16
N	19,98	19,90
O	5,77	5,82
S	11,43	11,44

Example 4

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine (6)

1,3-Di-n-butyl-2-thioxanthine (12,6 g) was treated with sodium (1,05 g) in absolute ethanol (45 ml) to give the 1-3-di-n-butyl-2-thioxanthine sodium salt by heating under reflux for one hour. 1-Bromo-propan-n-2-one (ml) was then added dropwise and the reaction mixture was heated under reflux for a further hour. After cooling to room temperature, the precipitated sodium bromide was filtered off and the solution was evaporated to dryness. The residue was dissolved in chloroform and treated with dilute NaOH to remove unreacted starting material. The chloroform phase was washed with water, dried, filtered and evaporated in vacuo to dryness. This residue was dissolved in methanol and treated with charcoal to remove the colour of the solution. After standing, the 1,3-di-n-butyl-7-(2-oxopropyl)-2-thioxanthine precipitated as a white powder.

Melting point: 131 - 132°C

Yield: 3,5 g

Elemental Analysis

	Calculated	Found
C	57,12	57,16
H	7,19	7,24
N	16,65	16,80
O	9,51	9,40
S	9,53	9,56

Example 5

1,3-Di-n-butyl-7-(2-oxopropyl)-6-thioxanthine (7)

1,3-Di-n-butyl-6-thioxanthine (5,6 g) was treated with sodium (0,46 g) in absolute ethanol (20 ml) to give the 1,3-di-n-butyl-6-thioxanthine sodium salt by heating under reflux for one hour. 1-chloropropan-2-one (2,31 g) dissolved in ethanol (20 ml) was added dropwise and the reaction mixture heated under reflux for a further 5 hours. The reaction was then complete (as judged by TLC). After standing overnight, the precipitated sodium chloride was filtered off under suction. The dark filtrate was extracted with chloroform. The chloroform phase was washed three times with 1N NaOH, washed with water, dried with sodium sulphate, filtered and the chloroform was removed in vacuo to yield a dark brown residue. On crystallisation from ethanol the residue gave 1,3-di-n-butyl-7-(2-oxo-propyl)-6-thioxanthine as a white powder.

Melting point: 152°C
Yield: 0,6 g

Elemental analysis:

	Calculated	Found
C	57,11	57,29
H	7,19	7,02
N	16,65	16,73
O	9,50	9,61
S	9,55	9,50

The structure was confirmed by NMR spectroscopy.

Using an analogous process the following two compounds were prepared:

1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-di-thioxanthine (8)

Melting point: 173°C
Yield: 1,2 g
crystallisation solvent: ethanol

Elemental analysis:

	Calculated	Found
C	54,52	54,64
H	6,86	6,81
N	15,89	15,93
O	4,54	4,74
S	18,19	17,87

The structure was confirmed by NMR spectroscopy.

1,3-Di-ethyl-7-(2-oxopropyl)-2-thioxanthine (9)

Melting point: 202°C
Yield: 7,9 g ≙ 41,9% of the theory
crystallisation solvent: ethanol

Elemental analysis:

	Calculated	Found
C	51,41	51,18
H	5,75	6,02
N	19,98	19,95
O	11,41	11,44
S	11,44	11,36

The structure was confirmed by NMR spectroscopy.

Example 12

Composition

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine, magnesium stearate and microcrystalline cellulose may be blended together and passed through a 40 mesh sieve (UK). The resulting mixture may be tabletted on a conventional rotary machine to produce a batch of 5000 tablets of the following composition:

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine	10 mg
magnesium stearate	0.2 mg
microcrystalline cellulose	189.8 mg

Pharmacology

Methodology

Cats of either sex were anaesthetized by i.p. injection of urethane/chloralose (120/60 mg/kg). The intraduodenal (i.d.) administration of compounds was conducted by means of a plastic catheter which was inserted into the duodenum following midline incision at the abdominal cavity.

i) pO_2-measurements

Measurement of muscle surface pO_2. The skin above the measuring site (3-4 mm in diameter) was removed and one multiwire-surface electrode (Eschweiler, Kiel) was placed on the gastrocnemius muscle of each hindlimb. The femoral artery in one hindlimb was ligated in order to induce ischaemia. Muscle temperature was controlled by means of a thermocouple (Ellab, Copenhagen). The electrode current was measured every 6 to 8 s and collected for periods of 4 min (Hewlett-Packard programmable data logger system 3051 A). After each period, mean value and standard deviation was calculated.

ii) Skeletal muscle contractility

After dissection of the skin of the calf muscles, the sciatic nerve was cut about 3 cm proximal to the knee. The tendon of the calf muscles was cut and connected with an isometric force transducer (SWEMA, SG 3). In order to maintain constant differences and a resting tension of 100 p in cats and 25 p in rats, the hindlimb was fixed at the tibia by means of a clamp. Direct stimulation of the muscles consisted of square wave pulses of 4 msec duration at a frequency of 2 Hz and at a voltage 50 V in cats. In order to keep the muscles

wet and at a normal temperature, the muscles were continuously superfused with 0.9% w/v NaCl solution (38°C). Femoral blood flow was restricted by a graded occlusion of the artery leading to a reduction of contractility by ca. 30 %. After having reached a constant level of the contraction force, the appropriate vehicle (NaCl or Methocel) was injected, followed by the test substance.

Results

i) pO_2-measurements

Compound	dosage (mg/kg) i.d.*	n	hypoxic tissue			normoxic tissue		
			C_s	$\overline{\Delta pO_2}$	E	C_s	$\overline{\Delta pO_2}$	E
1	12.5	2	1	1.4	1.4	1	12.9	12.9
3	12.5	3	0.67	3.8	2.7	1	7.0	7.0
	32.0	3	0.67	4.5	3.0	1	2.0	2.0
6	0.1	4	1	6.2	6.2	0.67	8.4	5.7
	0.3	4	1	5.3	5.3	1	5.7	5.7
8	2.0	4	0.75	6.6	5.0	0.5	9.9	4.9

ii) skeletal muscle contractility

Compound	dosage (mg/kg) i.d.*	n	average increase (%)^{o}
1	2.0	2	+22.2
	5.0	2	+12.1
3	12.5	2	+10.4
4	12.5	1	+7.1
	32.0	3	+21.1

Compound	(mg/kg) i.d.*	n	increase (%)^{p}
6	0.3	2	+ 5.3
	0.8	3	+ 7.5
	2.0	4	+10.3
	5.0	3	+17.1
9	32.0	2	+ 9.4

n = number of animals

C_s = significance coefficient = number of measuring sites with significant pO_2 increase per total number of measuring sites

$\overline{\Delta\ pO_2}$ = mean pO_2increase in experiments with significant pO_2 increase (Torr)

E = efficiency - index = $C_s \times \overline{\Delta pO_2}$ (Torr)

Control values : E between 0 and 1.4 Torr

* i.d. = intraduodenal application of a suspension in Methocel (methyl cellulose)

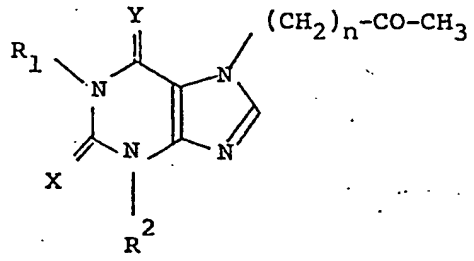
(%)° of initial values

Toxicty

No toxic effects were observed at the test dosages.

Claims

1. A compound of the formula (II):



(II)

characterised in that

X is sulphur and Y is oxygen or sulphur;

R_1 is an alkyl group of up to 6 carbon atoms;

R_2 is an alkyl group of up to 6 carbon atoms; and

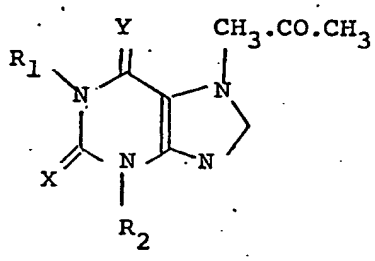
n is 1; or

X is oxygen and Y is sulphur;

one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms; and

n is 1 or 2; or a pro-drug therefor.

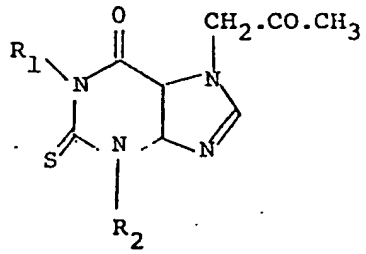
2. A compound according to claim 1 of the formula (III):



(III)

characterised in that R_1, R_2, X and Y are as defined in claim 1; or a pro-drug therefor.

3. A compound according to claim 1 of the formula (IV):

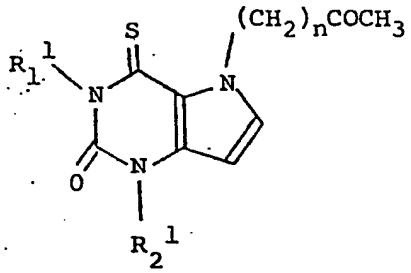


(IV)

characterised in that R_1 and R_2 are as defined in claim 1; or a pro-drug therefor.

4. 1,2-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine.

5. A compound according to claim 1 of the formula (V) or a pro-drug therefor:

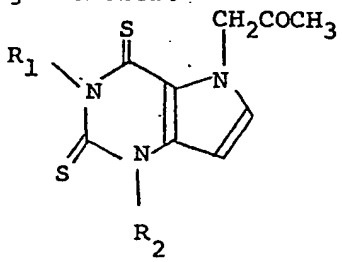


(V)

characterised in that n is as defined in claim 1, and one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms.

6. 1-n-Butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine or 1-n-butyl-3-ethyl-7-(3-oxobutyl)-6-thioxanthine.

7. A compound according to claim 1 of the formula (VI) or a pro-drug therefor:



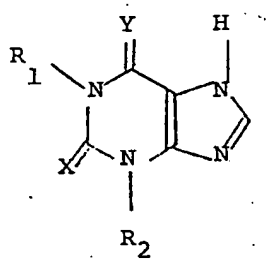
(VI)

characterised in that R_1 and R_2 are as defined in claim 1.

8. 1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-dithioxanthine.

9. A pharmaceutical composition, which composition comprises a compound according to claim 1 together with a pharmaceutically acceptable carrier.

10. A process for the preparation of a compound according to claim 1, characterised by the reaction of a salt of compound of the formula (VII):



(VII)

wherein R_1, R_2, X and Y are as defined in claim 1 with a compound of the formula (VIII):

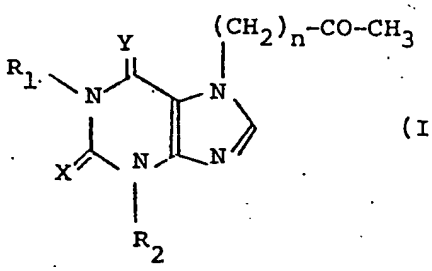
$$Cl-(CH_2)_n-CO-CH_3 \qquad (VIII)$$

wherein n is as defined in claim 2 or a chemical equivalent thereof, or, when n is 2 in the compound of the formula (II), with methyl vinyl ketone.

11. 1,3-Di-n-butyl-2-thioxanthine or 1,3-Di-n-butyl-2,6-dithioxanthine.

Claims

1. A process for the preparation of a compound of the formula (II):



(II)

wherein:

X is sulphur and Y is oxygen or sulphur;

R_1 is an alkyl group of up to 6 carbon atoms;

R_2 is an alkyl group of up to 6 carbon atoms; and

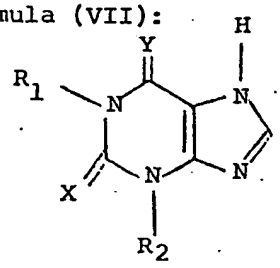
n is 1; or

X is oxygen and Y is sulphur;

one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 6 carbon atoms; and

n is 1 or 2;

characterised by the reaction of a salt of a compound of the formula (VII):



(VII)

wherein R_1, R_2, X and Y are as defined above with a compound of the formula (VIII):

$$Cl-(CH_2)_n-CO-CH_3 \qquad \text{(VIII)}$$

wherein n is as defined above or a chemical equivalent thereof, or, when n is 2 in the compound of the formula (II), with methyl vinyl ketone.

2. A process according to claim 1, characterised in that n is 1.

3. A process according to claim 2, characterised in that X is S and Y is O.

4. A process according to claims 2 and 3, characterised in that R_1 and R_2 are each n-butyl.

5. A process according to claim 1, characterised in that X is O and Y is S.

6. A process according to claim 5, characterised in that R_1 is n-butyl and R_2 is ethyl.

7. A process according to claim 1, characterised in that X and Y are both S.

8. A process according to claim 7, characterised in that R_1 and R_2 are each n-butyl.

9. A process for the preparation of 1,3-di-n-butyl-2-thioxanthine, characterised by the reaction of 4-amino-1,3-di-n-butyl-2-thiouracil with sodium carbonate, formamide, formic acid and sodium dithionite.

10. A process for the preparation of 1,3-di-n-butyl-2,6-dithioxanthine, characterised by the reaction of P_4S_{10} and 1,3-di-n-butyl-2-thioxanthine or 1,3-di-n-butyl-6-thioxanthine.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 80 30 1053.7

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	Chemical Abstracts vol. 57, no. 5, 3 September 1962 Columbus, Ohio, USA K.R.H. WOOLDRIDGE et al. "The synthesis of some 6-thioxanthines" column 5924 to 5926 * column 5925 h * & J. Chem Soc., 1962, pages 1863 to 1868 --	1,2,5
	FR - A - 1 167 425 (J.R. GEIGY) * formula III * --	1-3
	DE - A1 - 2 330 742 (CHEMISCHE WERKE ALBERT) * claim 2 * --	10
A	Chemical Abstracts vol. 85, no. 21, 22 November 1976 Columbus, Ohio, USA B. KOKEL et al. "A process for preparing α-ketols from diazomethyl ketones" page 487, column 2, abstract no. 159334p & C.R. Hebd. Seances Acad. Sci., Ser. C, vol. 282, no. 24, 1976, pages 1125 to 1127 (Fr) ----	

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 473/22
C 07 D 473/20
A 61 K 31/52

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

A 61 K 31/52
C 07 D 473/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	15-07-1980	FROELICH

EPO Form 1503.1 06.78

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 018 136**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **16.11.83**

(21) Application number: **80301053.7**

(22) Date of filing: **02.04.80**

(51) Int. Cl.³: **C 07 D 473/22,**
C 07 D 473/20,
A 61 K 31/52

(54) **Xanthine derivatives, a process for their preparation and their use in pharmaceutical compositions.**

(30) Priority: **05.04.79 GB 7912052**
05.06.79 GB 7919505

(43) Date of publication of application:
29.10.80 Bulletin 80/22

(45) Publication of the grant of the patent:
16.11.83 Bulletin 83/46

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

(56) References cited:
DE - A - 2 330 742
FR - A - 1 167 425

Chemical Abstracts vol. 57, no. 5, 3 September 1962 Columbus, Ohio, USA K.R.H. WOOLDRIDGE et al. "The synthesis of some 6-thioxanthines" column 5924 to 5926

Chemical Abstracts vol. 85, no. 21, 22 November 1976 Columbus, Ohio, USA B. KOKEL et al. "A process for preparing alpha-ketols from diazomethyl ketones" page 487, column 2, abstract no. 159334p

(73) Proprietor: **BEECHAM - WUELFING GmbH & Co. KG**
Stresemannallee 6 P.O. Box 25
D-4040 Neuss (DE)

(72) Inventor: **Goring, Joachim Ewald**
Sauerweinstrasse 25
3212 Gronau (Leine) (DE)

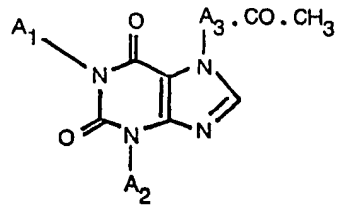
(74) Representative: **Russell, Brian John et al,**
European Patent Attorney Beecham Pharmaceuticals Great Burgh Yew Tree Bottom Road
Epsom Surrey, KT18 5XQ (GB)

EP 0 018 136 B1

Courier Press, Leamington Spa, England.

Xanthine derivatives, a process for their preparation and their use in pharmaceutical compositions

GB—A—1441562 discloses inter alia that compounds such as those of the formula (I):

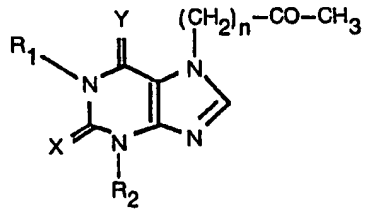


(I)

wherein A_1 and A_2 are alkyl groups and A_3 is an alkylene moiety possess blood flow improving properties. J. Chem. Soc., 1962, 1863 to 1868 discloses 7-acetylmethyl-1,3-dimethyl-6-thioxanthine and 7-acetylmethyl-3-isobutyl-1-methyl-6-thioxanthine as coronaro- and broncho-dilators. FR—A—1,167,425 generically discloses certain 2-thioxanthines only as intermediates.

It has now been found that a class of compounds yet further removed from naturally occurring xanthines effect an improvement in the metabolic status of ischaemic skeletal muscle by increasing oxygen tension and/or contractility in the tissue. The compounds are thus of potential use as agents for the treatment of peripheral vascular diseases such as intermittment claudication.

The present invention provides the structurally distinct compounds of the formula (II):



(II)

wherein:

X is a sulphur and Y is oxygen or sulphur;

R_1 is an alkyl group of up to 6 carbon atoms;

R_2 is an alkyl group of up to 6 carbon atoms; and

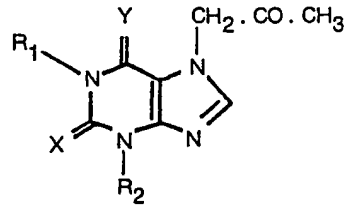
n is 1; or

X is oxygen and Y is sulphur;

one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 3 carbon atoms; and

n is 1 or 2;.

When n is 1 or 2, it is preferably 1. Thus, certain particularly suitable compounds of the formula (II) are those of the formula (III):



(III)

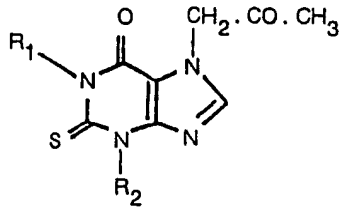
wherein R_1, R_2, X and Y are as defined in relation to formula (II);

Alkyl groups R_1 and R_2 worthy of mention for the compounds of the formulae (II) and (III) include the methyl ethyl, iso-propyl, n-butyl,iso-butyl, n-pentyl and n-hexyl groups.

Favourably in formulae (II) and (III) R_1 and R_2 together contain 3—10 carbon atoms and more favourably they together contain 4, 5, 6, 7 or 8 carbon atoms.

Aptly Y in the compounds of the formulae (II) and (III) is an oxygen atom and X is a sulphur atom.

Thus certain favoured compounds of this invention include those of the formula (IV),



(IV)

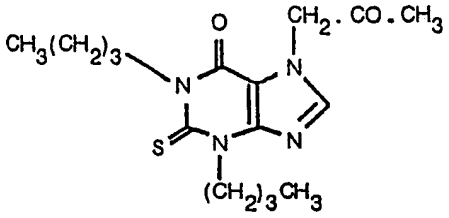
wherein R_1 and R_2 are as defined in formula (II).

Alkyl groups R_1 and R_2 worthy of mention and favourable total carbon atom numbers thereof are as to described under formula (III).

A preferred value for R_1 in formula (IV) is the n-butyl group. Ethyl is also of interest.

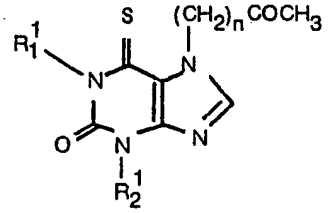
A preferred value for R_2 in formula (IV) is the n-butyl group. Ethyl is also of interest.

From the foregoing it will be appreciated that one compound possessing particularly suitable properties is that of the formula



Also aptly Y in the compounds of the formula (II) is a sulphur atom and X is an oxygen atom.

Thus certain other favoured compounds of this invention include those of the formula (V)



(V)

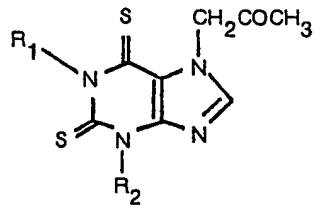
wherein n is as defined in relation to formula (II); and one of R_1^1 and R_2^1 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 or 3 carbon atoms.

Suitable groups R_1^1 and R_2^1 as appropriate include ethyl, iso-propyl, n-butyl, isobutyl, n-pentyl and n-hexyl.

Favourably R_1^1 and R_2^1 together contain 4, 5, 6, 7 or 8 carbon atoms.

Preferably R_1 is butyl and R_2 is ethyl.

Other compounds of this invention are of the formula (VI),



(VI)

wherein R_1 and R_2 are as defined in relation to formula (II).

Alkyl groups R_1 and R_2 worthy of mention and favourable total carbon atom numbers therefor are as so described under formula (III).

Preferably R_1 and R_2 are both n-butyl.

Compounds of the formula (II) have useful pharmacological activity, as disclosed hereinbefore, in effecting an improvement in the metabolic status of ischaemic skeletal muscle, by increasing oxygen tension or contractility in the tissue.

Individual compounds of the formula (II) have one or both of these activities. The individual

activity profile may be readily ascertained by the two routine pharmacological tests disclosed hereinafter. Nevertheless examples of compounds of interest for each or both activities are given here:

Examples of compounds of the formula (II) which are of particular interest for their activity in increasing ischaemic skeletal muscle contractility are those of the formulae (IV) and (V).

Examples of compounds of the formula (II) which are of particular interest for their activity in increasing oxygen tension in ischaemic skeletal muscle are those of the formula (VI), in particular 1,3-di-n-butyl-7-(2-oxopropyl)-2,6-thioxanthine.

Examples of the compounds of the formula (II) which are of particular interest for both of the foregoing activities are those of the formulae (IV) and (V) having the preferred variable values so described under the relevant formula.

As mentioned hereinbefore the compounds of the formula (II), which have either or both of these activities are of potential use for the treatment of peripheral vascular diseases, such as intermittant claudication.

The present invention therefore also provides a pharmaceutical composition which comprises a compound of the formula (II) or a pro-drug therefor and a pharmaceutically acceptable carrier.

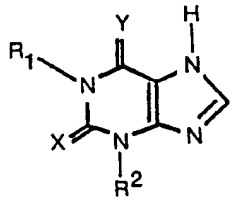
The composition of this invention will normally be provided in the form of a discrete unit dose such as a tablet, capsule or defined quantity of the composition in a form suitable for dissolution to provide an injectable solution. Particularly suitable forms of such compositions are those adapted for oral administration such as tablets or capsules.

Unit dose compositions of this invention may contain 1 to 500 mgs of active agent. Compounds of this invention wherein the 7-position side chain is other than 2-oxo-propyl or a group convertable thereto will normally be present in such compositions in a dose from 100 to 500 mgs, for example 200 to 400 mgs. Compounds of this invention wherein the 7-position side chain is 2-oxopropyl or a group convertable thereto will normally be present in such compositions in a dose from 1 to 100 mgs, more usually 2.5 to 50 mgs for example 5 to 25 mgs. The unit dose composition will normally be taken from 1 to 4 times daily so that the normal dose for a 70 kg adult human will be from about 100 to 2000 mgs for a composition containing a compound in which the 7-position substituent is other than 2-oxopropyl or a group convertable thereto and from about 4 to 100 mgs for a composition containing a compound in which the 7-position substituent is a 2-oxopropyl group or a group convertable thereto.

The compositions of this invention may be formulated in conventional manner. Thus oral dosage units may contain such conventional agents as fillers (diluents), lubricants, binders, disintegrants, colourants, flavourings, surface active agents, preservatives, buffering agents, and the like. Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate and the like. Suitable lubricants include stearic acid, magnesium stearate, magnesium lauryl sulphate and the like. Injectable compositions may consist essentially of a sterile, pyrogen free compound of this invention sealed into a vial optionally together with suspending and preserving agents. Such compositions may be made up for administration with sterile water or saline.

The compositions may be prepared by conventional methods of blending, filling, tabletting or the like.

The present invention also provides a process for the preparation of the compounds of this invention which process comprises the reaction of a salt of a compound of the formula (VII):



(VII)

wherein R_1, R_2, X and Y are as defined in relation to formula (II) with a compound of the formula (VIII):

$$Cl—(CH_2)_n—CO—CH_3 \qquad (VIII)$$

wherein n and m are as defined in relation to formula (II) or a chemical equivalent thereof.

Suitable chemical equivalents of the chloro-compound of the formula (VIII) include the corresponding bromo- and iodo-compounds and analogous active esters such as mesylates or tosylates.

The salt of the compound of the formula (VII) will normally be an alkali metal salt such as the sodium or potassium salt and may be preformed or generated in situ by the presence of a base such as an hydroxide or ethanolate.

Suitable solvents for use in such processes include lower alkanols such as methanol, ethanol or the like.

The reaction is generally carried out at an ambient or elevated temperature, for example from 20° to 80°C. It is often convenient to carry out the reaction in a solvent under reflux.

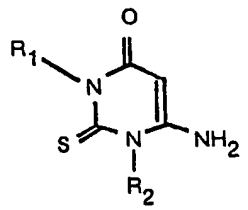
When the desired compound has been produced it may be recovered by distilling off the solvent, by precipitation with a miscible non-solvent or the like.

Purification of the compound of this invention may be carried out by conventional methods such as crystallisation, recrystallation and chromatography.

Compounds of the formula (II) wherein n is 2 may be prepared by the reaction of a compound of the formula (VII) with methyl vinyl ketone or 2-chlorobutan-3-one. This reaction may be carried out under conditions as described herein for reaction with a compound of the formula (VIII).

Compounds of the formula (VII) wherein Y is a sulphur atom and X is an oxygen atom may be prepared by the process by of K.R.H. Wooldrige and R. Slack, J. Chem. Soc., 1962, 1863—68.

The compounds of the formula (VII) wherein X is a sulphur atom and Y is an oxygen atom may be prepared by the reaction of a compound of the formula (IX):



(IX)

wherein R_1 and R_2 are as defined in relation to formula (II) with sodium carbonate, formamide, formic acid and sodium dithionite. This reaction is generally begun at a depressed temperature such as 3—5°C and gradually warmed until completion occurs at an elevated temperature such as 160—190°C.

The compounds of formula (IX) may be prepared according to the procedures of Bredeneck et al., Chem. Ber., 88, 1306—1312 (1955). Their conversion into compounds of the formula (VIII) as described above may be viewed in the light of Papesch et al., US—A—2615020.

Compounds of the formula (VII) wherein X and Y are both sulphur atoms may be prepared by the reaction of P_4S_{10} and a compound of the formula (VIII) wherein one of X and Y is a sulphur atom and the other is an oxygen atom or both of X and Y are oxygen atoms; see for example US—A—3135753, Chem. Zentralblatt 37—2695 (1966), Chem. Zentralblatt 27—1557 (1966) and Chem. Zentralblatt 40—0983 (1968).

The following Examples illustrate the invention.

Example 1

1-n-Butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine (1)

1-n-Butyl-3-ethyl-6-thioxanthine (4 g) was dissolved in dimethyl formamide (30 ml) and a small amount of potassium carbonate was added. To this mixture, 1-bromopropan-2-one (2,7 g) was added dropwise at room temperature, with stirring. The reaction was heated at about 50°C for two hours. The reaction mixture was then extracted with chloroform several times, the chloroform phase washed with 1N KOH and water, dried with sodium sulphate, filtered and the chloroform removed in vacuo to yield a red/brown oil which, on crystallisation in a mixture of ethylacetate/petroleum, gave *1-n-butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine* as a white powder.

Melting point: 173—174°C

Yield: 1 g

Elemental Analysis

	Calculated	Found
C	54,55	55,14
H	6,49	6,34
N	18,19	17,89
O	10,39	10,60
S	10,39	10,01

Example 2

1-n-butyl-3-ethyl-7-(3-oxobutyl)-6-thioxanthine (2)

1,3-di-n-butyl-6-thioxanthine (8,3 g), methylvinylketone (2,9 ml) and triethylamine (1 ml) were dissolved in ethanol (10 ml) and the mixture was slowly heated with stirring at 40—50°C for one hour. After cooling of the clear solution, the *1,3-di-n-butyl-7-(3-oxobutyl)-6-thioxanthine* precipitated in the form of yellow needles.

Melting point: 118—119°C
Yield: 8,5 g
Elemental Analysis

	Calculated	Found
C	58,29	58,28
H	7.43	7.40
N	16,00	16,12
O	9,14	9,27
S	9,14	8,90

The structure was confirmed by NMR spectroscopy.

Using an alalogous process *1-n-butyl-3-ethyl-7-(3-oxobutyl)-6-thioxanthine (2)* m.pt. 127°C, was prepared in 75% yield. The crystalisation solvent was ethanol.

	Elemental Analysis				
	C %	H %	N %	O %	S %
Calculated	55,90	6,83	17,39	9,94	9,94
Found	56,08 55,95	6,91 6,92	16,91 17,03	10,23 10,35	9,87 9,85

Example 3

1,3-Di-n-butyl-2-thioxanthine

Sodium carbonate (8 g) was dissolved in formamide (200 ml) and 1,3-di-n-butyl-2-thio-4-aminouracil (32 g) was added at a temperature of 3°C with stirring. The mixture was cooled over a period of 1 hour and at a temperature of 3—5°C. Formic acid (16 ml) was added dropwise. The reaction mixture was allowed to stand overnight in a refrigerator. The mixture was then heated to 100°C and then sodium dithionite (5 g) was added at this temperature. To complete the reaction, the mixture was heated to 190°C for 1 hour. After cooling to room temperature with stirring, the oil solidified with crystallisation. The crude product was filtered with suction. To remove coloured by-products, the crude product was dissolved in dilute sodium hydroxide, the solution treated with charcoal and precipitated with acetic acid and the compound was recrystallised from methanol/water to give *1,3-di-n-butyl-2-thioxanthine* as white powder.

Melting point: 137°C
Yield: 27,2 g
Elemental Analysis

	Calculated	Found
C	55,69	55,76
H	7,19	7,16
N	19,98	19,90
O	5,77	5,82
S	11,43	11,44

Example 4

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine (3)

1,3-Di-n-butyl-2-thioxanthine (12,6 g) was treated with sodium (1,05 g) in absolute ethanol (45 ml) to give the 1,3-di-n-butyl-2-thioxanthine sodium salt by heating under reflux for one hour. 1-Bromo-propan-n-2-one (ml) was then added dropwise and the reaction mixture was heated under reflux for a further hour. After cooling to room temperature, the precipitated sodium bromide was filtered off and the solution was evaporated to dryness. The residue was dissolved in chloroform and treated with dilute NaOH to remove unreacted starting material. The chloroform phase was washed with water, dried, filtered and evaporated in vacuo to dryness. This residue was dissolved in methanol and treated with charcoal to remove the colour of the solution. After standing the *1,3-di-n-butyl-7-(2-oxopropyl)-2-thioxanthine* precipitated as a white powder.

Melting point: 131—132°C
Yield: 3,5 g
Elemental Analysis

	Calculated	Found
C	57,12	57,16
H	7,19	7,24
N	16,65	16,80
O	9,51	9,40
S	9,53	9,56

1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-di-thioxanthine (4)

Melting point: 173°C
Yield: 1,2 g
crystallisation solvent: ethanol
Elemental Analysis

	Calculated	Found
C	54,52	54,64
H	6,86	6,81
N	15,89	15,93
O	4,54	4,74
S	18,19	17,87

The structure was confirmed by NMR spectroscopy.

1,3-Di-ethyl-7-(2-oxopropyl)-2-thioxanthine (5)

Melting point: 202°C
Yield: 7,9 g ≙ 41,9% of the theory
crystallisation solvent: ethanol
Elemental Analysis

	Calculated	Found
C	51,41	51,18
H	5,75	6,02
N	19,98	19,95
O	11,41	11,44
S	11,44	11,36

The structure was confirmed by NMR spectroscopy.

Example 5

Composition

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine, magnesium stearate and microcrystalline cellulose may be blended together and passed through a 40 mesh sieve (UK). The resulting mixture may be tabletted on a conventional rotary machine to produce a batch of 5000 tablets of the following composition:

1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthine	10 mg
magnesium stearate	0.2 mg
microcrystalline cellulose	189.8 mg

Pharmacology

Methodology

Cats of either sex were anaesthetized by i.p. injection of urethane/choralose (120/60 mg/kg). The intraduodenal (i.d.) administration of compounds was conducted by means of a plastic catheter which was inserted into the duodenum following midline incision at the abdominal cavity.

i) pO_2-measurements

Measurement of muscle surface pO_2. The skin above the measuring site (3—4 mm in diameter) was removed and one multiwire-surface electrode (Eschweiler, Kiel) was placed on the gastrocnemius muscle of each hindlimb. The femoral artery in one hindlimb was ligated in order to induce ischaemia. Muscle temperature was controlled by means of a thermocouple (Ellab, Copenhagen). The electrode current was measured every 6 to 8 s and collected for periods of 4 min (Hewlett-Packard programmable data logger system 3051 A). After each period, mean value and standard deviation was calculated.

ii) Skeletal muscle contractility

After dissection of the skin of the calf muscles, the sciatic nerve was cut about 3 cm proximal to the knee. The tendon of the calf muscles was cut and connected with an isometric force transducer (SWEMA, SG 3). In order to maintain constant differences and a resting tension of 100 p in cats and 25 p in rats, the hindlimb was fixed at the tibia by means of a clamp. Direct stimulation of the muscles consisted of square wave pulses of 4 msec duration at a frequency of 2 Hz and at a voltage 50 V in cats. In order to keep the muscles wet and at a normal temperature, the muscles were continuously superfused with 0.9% w/v NaCl solution (38°C). Femoral blood flow was restricted by a graded occlusion of the artery leading to a reduction of contractility by ca. 30%. After having reached a constant level of the contraction force, the appropriate vehicle (NaCl or Methocel) was injected, followed by the test substance.

Results

i) pO_2-measurements

Compound	dosage (mg/kg) i.d.*	n	hypoxic tissue			normoxic tissue		
			C_s	$\overline{\Delta pO_2}$	E	C_s	$\overline{\Delta pO_2}$	E
1	12.5	2	1	1.4	1.4	1	12.9	12.9
2	12.5	3	0.67	3.8	2.7	1	7.0	7.0
	32.0	3	0.67	4.5	3.0	1	2.0	2.0
3	0.1	4	1	6.2	6.2	0.67	8.4	5.7
	0.3	4	1	5.3	5.3	1	5.7	5.7
4	2.0	4	0.75	6.6	5.0	0.5	9.9	4.9

ii) skeletal muscle contactility

Compound	dosage (mg/kg) i.d.*	n	average increase (%)°
1	2.0	2	+22.2
	5.0	2	+12.1
2	12.5	2	+10.4

Compound	(mg/kg) i.d.*	n	increase (%)°
3	0.3	2	+ 5.3
	0.8	3	+ 7.5
	2.0	4	+10,3
	5.0	3	+17.1
5	32.0	2	+ 9.4

n = number of animals

C_s = significance coefficient = number of measuring sites with significant pO_2 increase per total number of measuring sites.

$\overline{\Delta pO_2}$ = mean pO_2 increase in experiments with significant pO_2 increase (Torr)

E = efficiency – index = $C_s \times \overline{\Delta pO_2}$ (Torr)

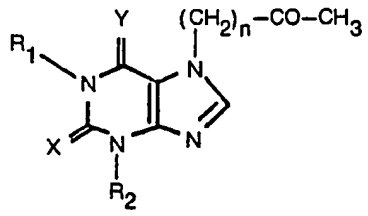
Control values : E between 0 and 1.4 Torr
* i.d. = intraduodenal application of a suspension in Methocel (methyl cellulose)
(%)° of initial values.

Toxicity

No toxic effects were observed at the test dosages.

Claims

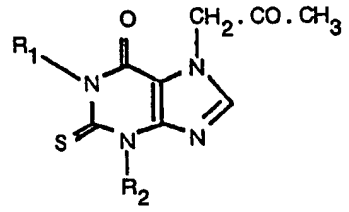
1. A compound of the formula (II):



(II)

characterised in that
X is sulphur and Y is oxygen or sulphur:
R_1 is an alkyl group of up to 6 carbon atoms;
R_2 is an alkyl group of up to 6 carbon atoms; and
n is 1; or
X is oxygen and Y is sulphur;
one of R_1 and R_2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 to 3 carbon atoms; and
n is 1 or 2.

2. A compound according to claim 1 of the formula (IV) in solid form:



(IV)

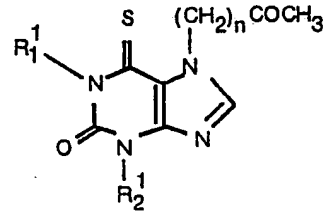
characterised in that R_1 and R_2, are as defined in claim 1.

3. A compound according to claim 2 of formula (IV) in essentially pure form.

4. A compound according to claim 2 of formula (IV) for use in the treatment of peripheral vascular disease.

5. A compound according to any one of claims 2, 3 and 4 which is 1,3-di-n-butyl-7-(2-oxopropyl)-2-thioxanthine.

6. A compound according to claim 1 of the formula (V) or

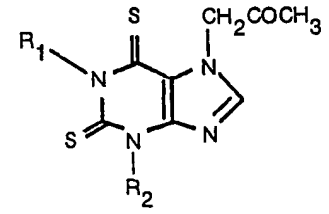


(V)

characterised in that n is as defined in claim 1, and one of R_1^1 and R_2^2 is an alkyl group of up to 6 carbon atoms and the other is an alkyl group of 2 or 3 carbon atoms.

7. 1-n-Butyl-3-ethyl-7-(2-oxopropyl)-6-thioxanthine or 1-n-butyl-3-ethyl-7-(3-ethyl-7-(3-oxo-butyl)-6-thioxanthine.

8. A compound according to claim 1 of the formula (VI):



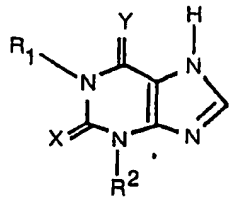
(VI)

characterised in that R_1 and R_2 are as defined in claim 1.

9. 1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-dithioxanthine.

10. A pharmaceutical composition, which composition comprises a compound according to claim 1 together with a pharmaceutically acceptable carrier.

11. A process for the preparation of a compound according to claim 1, characterised by the reaction of a salt of compound of the formula (VII):



(VII)

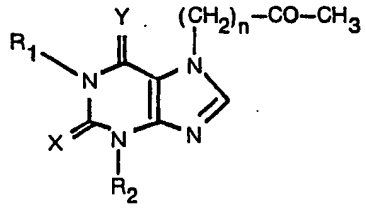
wherein R_1, R_2, X and Y are as defined in claim 1 with a compound of the formula (VIII):

$$Cl—(CH_2)_n—CO—CH_3 \qquad (VIII)$$

wherein n is as defined in claim 2 or a chemical equivalent thereof, or, when n is 2 in the compound of the formula (II), with methyl vinyl ketone.

Revendications

1. Composé de formule (II):



(II)

caractérisé en ce que

X est du soufre et Y est de l'oxygène ou du soufre;

R_1 est un groupe alcoyle jusqu'à 6 atomes de carbone;

R_2 est un groupe alcoyle ayant jusqu'à 6 atomes de carbone; et

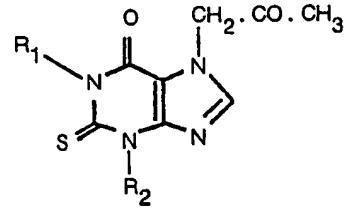
n est égal à 1; ou

X est de l'oxygène et Y est du soufre;

l'un des groupes R_1 et R_2 est un groupe alcoyle ayant jusqu'à 6 atomes de carbone et l'autre est un groupe alcoyle ayant 2 à 3 atomes de carbone; et

n est égal à 1 ou 2.

2. Composé suivant la revendication 1 de formule (IV) sous forme solide:



(IV)

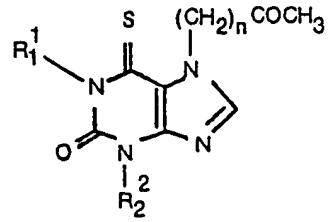
caractérisé en ce que R_1 et R_2 sont tels que définis dans la revendication 1.

3. Composé suivant la revendication 2 de formule (IV) sous forme essentiellement pure.

4. Composé suivant la revendication 2 de formule (IV) destiné à être utilisé pour le traitement des affections vasculaires périphériques.

5. Composé suivant l'une quelconque des revendications 2, 3 et 4, constitué par la 1,3-di-n-butyl-7-(2-oxopropyl)-2-thioxanthine.

6. Composé suivant la revendication 1 de formule (V):

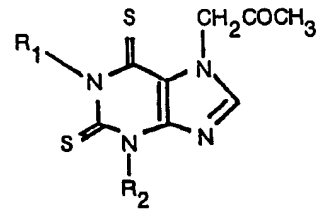


(V)

caractérisé en ce que n est tel que défini dans la revendication 1, et l'un des groupes R_1^1 et R_2^2 est un groupe alcoyle ayant jusqu'à 6 atomes de carbone et l'autre est un groupe alcoyle ayant 2 ou 3 atomes de carbone.

7. 1-n-Butyl-3-éthyl-7-(2-oxopropyl)-6-thioxanthine ou 1-n-butyl-3-éthyl-7-(3-oxobutyl)-6-thioxanthine.

8. Composé suivant la revendication 1 de formule (VI):



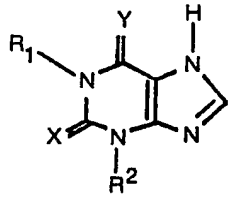
(VI)

caractérisé en ce que R_1 et R_2 sont tels que définis dans la revendication 1.

9. 1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-dithioxanthine.

10. Composition pharmaceutique renfermant un composé suivant la revendication 1, conjointement à un véhicule ou excipient pharmaceutiquement acceptable.

11. Procédé pour la préparation d'un composé suivant la revendication 1, caractérisé par la réaction d'un sel du composé de formule (VII):



(VII)

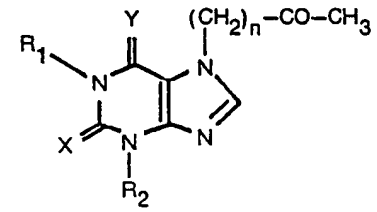
dans laquelle R_1, R_2, X et Y sont tels que définis dans la revendication 1, avec un composé de formule (VIII):

$$Cl—(CH_2)_n—CO—CH_3 \qquad \text{(VIII)}$$

dans laquelle n est tel que défini dans la revendication 2 ou un équivalent chimique de celui-ci, ou bien, quand n est égal à 2 dans le composé de formule (II), avec de la méthylvinylcétone.

Patentansprüche

1. Eine Verbindung der Formel (II):

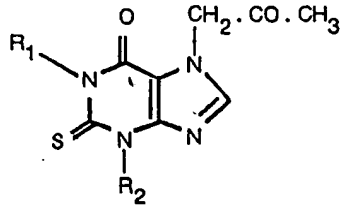


(II)

dadurch gekennzeichnet, daß

X Schwefel und Y Sauerstoff oder Schwefel ist;
R_1 eine Alkylgruppe mit bis zu 6 Kohlenstoffatomen ist;
R_2 eine Alkylgruppe mit bis zu 6 Kohlenstoffatomen ist; und
n 1 ist; oder
X Sauerstoff und Y Schwefel ist;
eine der Gruppen R_1 und R_2 eine Alkylgruppe mit bis zu 6 Kohlenstoffatomen und die andere eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen ist; und
n 1 oder 2 ist.

2. Eine Verbindung gemäß Anspruch 1 der Formel (IV) in Form eines Feststoffes:



(IV)

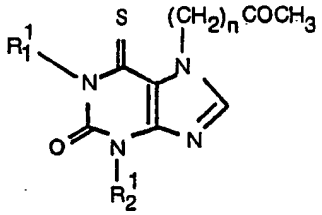
dadurch gekennzeichnet, daß R_1 und R_2 wie in Anspruch 1 definiert sind.

3. Eine Verbindung gemäß Anspruch 2 der Formel (IV) in im wesentlichen reiner Form.

4. Eine Verbindung gemäß Anspruch 2 der Formel (IV) zur Anwendung bei der Behandlung von kreislaufbedingten Gefäßerkrankungen.

5. Eine Verbindung gemäß irgendeinem der Ansprüche 2, 3 und 4 welche 1,3-Di-n-butyl-7-(2-oxopropyl)-2-thioxanthin ist.

6. Eine Verbindung gemäß Anspruch 1 der Formel (V):

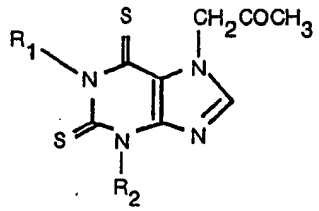


(V)

dadurch gekennzeichnet, daß n wie in Anspruch 1 definiert ist, und eine der Gruppen R_1^1 und R_2^2 eine Alkylgruppe mit bis zu 6 Kohlenstoffatomen und die andere eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen ist.

7. 1-n-Butyl-3-äthyl-7-(2-oxopropyl)-6-thioxanthin oder 1-n-Butyl-3-äthyl-7-(3-äthyl-7-(3-oxobutyl)-6-thioxanthin.

8. Eine Verbindung gemäß Anspruch 1 der Formel (VI)



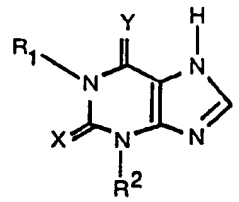
(VI)

dadurch gekennzeichnet, daß R_1 und R_2 wie in Anspruch 1 definiert sind.

9. 1,3-Di-n-butyl-7-(2-oxopropyl)-2,6-dithioxanthin.

10. Eine pharmazeutische Zusammensetzung, welche Zusammensetzung eine Verbindung gemäß Anspruch 1 zusammen mit einem pharmazeutischen verträglichen Träger enthält.

11. Ein Verfahren zur Herstellung einer Verbindung gemäß Anspruch 1, gekennzeichnet durch die Umsetzung eines Salzes der Verbindung der Formel (VII):



(VII)

in welcher R_1, R_2, X und Y wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel (VIII):

$$Cl—(CH_2)_n—CO—CH_3 \qquad (VIII)$$

in welcher n wie in Anspruch 2 definiert ist, oder einem chemischen Äquivalent davon, oder, wenn n in der Verbindung der Formel (II) 2 bedeutet, mit Methylvinylketon.